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May 31, 2002

WRITER'S DIRECT NUMBER:
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Art Unit 1632

Commissioner for Patents
Washington, D.C. 20231

Re: U.S. Utility Patent Application
Appl. No. 10/052,817; Filed: January 23, 2002
For: **Alpha-2-Macroglobulin Therapies and Drug Screening Methods for
Alzheimer's Disease**
Inventors: Tanzi *et al.*
Our Ref: 0609.4460005/JAG/FRC

Sir:

Transmitted herewith for appropriate action are the following documents:

1. Information Disclosure Statement;
2. Listing of the cited documents on Form PTO-1449 (30 sheets);
3. A copy of each of the one-hundred and one (101) cited documents on Form PTO-1449; and
4. Return postcard.

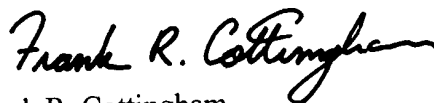
It is respectfully requested that the attached postcard be stamped with the date of filing of these documents, and that it be returned to our courier. In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

Commissioner for Patents
May 31, 2002
Page 2

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Frank R. Cottingham
Attorney for Applicants
Registration No. 50,437

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Enclosures

SKGF_DC1:18622.1



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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In re application of:

Tanzi *et al.*

Appl. No. 10/052,817

Filed: January 23, 2002

For: **Alpha-2-Macroglobulin Therapies
and Drug Screening Methods for
Alzheimer's Disease**

Confirmation No. 4182

Art Unit: 1632

Examiner: *To be assigned*

Atty. Docket: 0609.4460005/JAG/FRC

Information Disclosure Statement

Commissioner for Patents
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. A copy of each of these documents is provided.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

The Examiner is referred to the following related, co-pending patent application:

U.S. Patent Application No. 60/337,434, filed November 9, 2001, inventors Becker *et al.*, submitted herewith as Document **AT30**.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not

be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

Document **AS30** is the International Search Report for International Application No. PCT/US00/02412, which corresponds to the captioned U.S. Application.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith. It is further understood that the Examiner will consider information that had been cited or submitted to the U.S. Patent and Trademark Office in a prior application relied on under 35 U.S.C. § 120. 1138 OG 37, 38 (May 19, 1992).

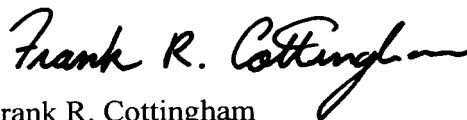
It is respectfully requested that the Examiner initial and return a copy of the enclosed PTO-1449, and to indicate in the official file wrapper of this patent application that the documents have been considered.

This Information Disclosure Statement is being filed more than three months after the filing date, but before the mailing date of a first Office Action on the merits. No statement or fee is required.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Frank R. Cottingham
Attorney for Applicants
Registration No. 50,437

Date: 5/31/02

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FORM PTO-1449

INFORMATION DISCLOSURE STATEMENT

ATTY. DOCKET NO.
0609.4460005/JAG/FRCAPPLICATION NO.
10/052,817APPLICANT
Tanzi et al.FILING DATE
01/23/2002GROUP
1632

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
	AA1	4,683,195	07/28/1987	Mullis et al.	435	6	02/07/1986
	AB1	5,830,670	11/03/1998	de la Monte et al.	435	7.2	05/30/1995
	AC1	5,948,634	09/07/1999	de la Monte et al.	435	69.1	11/14/1994
	AD1	5,948,888	09/07/1999	de la Monte et al.	530	350	05/30/1995
	AE1	6,071,705	06/06/2000	Wands et al.	435	7.1	06/06/1995
	AF1	6,156,311	12/05/2000	Strickland et al.	424	130.1	07/26/1996
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FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AL1	WO 91/03557	03/21/1991	WIPO			Yes No
	AM1	WO 92/03474	03/05/1992	WIPO			Yes No
	AN1	WO 96/39834	12/19/1996	WIPO			Yes No
	AO1	WO 97/04794	02/13/1997	WIPO			Yes No
	AP1	WO 99/11824	03/11/1999	WIPO			Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>1</u>	"Freely Associating," Nat. Genet. 22:1-2, Nature America, Inc. (May 1999).
	AS	<u>1</u>	Alvarez, V. et al., Association between an $\alpha 2$ Macroglobulin DNA Polymorphism and Late-Onset Alzheimer's Disease," Biochem. Biophys. Res. Commun. 264:48-50, Academic Press, Inc. (October 1999).
	AT	<u>1</u>	Andersen, G.R. et al., "Low Resolution X-Ray Structure of Human Methylamine-treated $\alpha 2$ -Macroglobulin," J. Biol. Chem. 270:25133-25141, American Society for Biochemistry and Molecular Biology, Inc. (1995).
EXAMINER			DATE CONSIDERED

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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>2</u>	Barrett, A.J. et al., "The Electrophoretically 'Slow' and 'Fast' Forms of the α 2-Macroglobulin Molecule," <i>Biochem. J.</i> 181:401-418, Portland Press, Ltd. (1979).
	AS	<u>2</u>	Bauer, J. et al., "Interleukin-6 and α 2-macroglobulin indicate an acute-phase state in Alzheimer's disease cortices," <i>FEBS Lett.</i> 285:111-114, Elsevier Science Publisher B.V. (1991).
	AT	<u>2</u>	Blacker, D. et al., "Correspondence," <i>Nat. Genet.</i> 22:21-22, Nature America, Inc. (May 1999).

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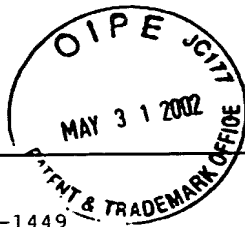
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	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	3	Blacker, D. et al., "Alpha-2 macroglobulin is genetically associated with Alzheimer disease," <i>Nat. Genet.</i> 19:357-360, Nature America, Inc. (August 1998).
	AS	3	Blennow, K. et al., "No association between the α 2-macroglobulin (A2M) deletion and Alzheimer's disease, and no change in A2M mRNA, protein, or protein expression," <i>J. Neural. Transm.</i> 107:1065-1079, Springer-Verlag (August 2000).
	AT	3	Boado, R.J., "Antisense drug delivery through the blood-brain barrier," <i>Adv. Drug Deliv. Rev.</i> 15:73-107, Elsevier Science Publishers B.V. (1995).

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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	4	Boado, R.J. et al., "Drug delivery of Antisense Molecules to the Brain for Treatment of Alzheimer's Disease and Cerebral AIDS," <i>J. Pharm. Sci.</i> 87:1308-1315, American Pharmaceutical Association (November 1998).
	AS	4	Borth, W., "α2-Macroglobulin, a multifunctional binding protein with targeting characteristics," <i>FASEB J.</i> 6:3345-3353, FASEB (1992).
	AT	4	Bowen, M.E. and Gettins, P.G.W., "Bait Region Involvement in the Dimer-Dimer Interface of Human α2-Macroglobulin and in Mediating Gross Conformational Change," <i>J. Biol. Chem.</i> 273:1825-1831, American Society for Biochemistry and Molecular Biology, Inc. (January 1998).

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	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>5</u>	Bretaudiere, J-P. et al., "Structure of native α 2-macroglobulin and its transformation to the protease bound form," <i>Proc. Natl. Acad. Sci. USA</i> 85:1437-1441, National Academy Press (1988).
	AS	<u>5</u>	Businaro, R. et al., "Synthesis and secretion of α 2-macroglobulin by human glioma established cell lines," <i>Exp. Brain Res.</i> 88:213-218, Springer-Verlag (1992).
	AT	<u>5</u>	Cavus, I. et al., "Inhibition of Long-Term Potentiation Development in Rat Hippocampal Slice by α 2-Macroglobulin, an Acute-Phase Protein in the Brain," <i>J. Neurosci. Res.</i> 43:282-288, Wiley-Liss, Inc. (February 1996).

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	AL						Yes No
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	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>6</u>	Chen, L. et al., "Apolipoprotein E promoter and α 2-Macroglobulin polymorphisms are not genetically associated with Chinese late onset Alzheimer's Disease," <i>Neurosci. Lett.</i> 269:173-177, Elsevier Science Ireland, Ltd. (July 1999).
	AS	<u>6</u>	Crawford, F. et al., "The alpha-2 macroglobulin gene is not associated with Alzheimer's disease in a case-control sample," <i>Neurosci. Lett.</i> 270:133-136, Elsevier Science Ireland, Ltd. (August 1999).
	AT	<u>6</u>	Dodel, R.C. et al., " α 2-Macroglobulin and the risk of Alzheimer's disease," <i>Neurology</i> 54:438-442, Lippincott, Williams & Wilkins (January 2000).

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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	1	Dow, D.J. et al., "α2-macroglobulin polymorphism and Alzheimer disease risk in the UK," <i>Nat. Genet.</i> 22:16-17, Nature America, Inc. (May 1999).
	AS	1	Du, Y. et al., "α2-Macroglobulin Attenuates β-Amyloid Peptide 1-40 Fibril Formation and Associated Neurotoxicity of Cultured Fetal Rat Cortical Neurons," <i>J. Neurochem.</i> 70:1182-1188, Lippincott-Raven Publishers (March 1998).
	AT	1	Du, Y. et al., "α2-Macroglobulin as a β-Amyloid Peptide-Binding Plasma Protein," <i>J. Neurochem.</i> 69:299-305, Lippincott-Raven Publishers (July 1997).

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FORM PTO-1

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	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	8	Fakler, B. <i>et al.</i> , "Short Antisense Oligonucleotide-mediated Inhibition Is Strongly Dependent on Oligo Length and Concentration but Almost Independent of Location of the Target Sequence," <i>J. Biol. Chem.</i> 269:16187-16194, American Society for Biochemistry and Molecular Biology, Inc. (1994).
	AS	8	Feldman, S.R. <i>et al.</i> , "Model of $\alpha 2$ -Macroglobulin structure and function," <i>Proc. Natl. Acad. Sci. USA</i> 82:5700-5704, National Academy Press (1985).
	AT	8	Gauderman, W.J. <i>et al.</i> , "Family-Based Association Studies," <i>J. Natl. Cancer Inst. Monogr.</i> 26:31-37, Oxford University Press (December 1999).

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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	9	Gliemann, J., "Receptors of the Low Density Lipoprotein (LDL) Receptor Family in Man. Multiple Functions of the Large Family Members via Interaction with Complex Ligands," <i>Biol. Chem.</i> 379:951-964, Walter de Gruyter and Company (August/September 1998).
	AS	9	Hampe, J. et al., "Mapping Genes for Polygenic Disorders: Considerations for Study Design in the Complex Trait of Inflammatory Bowel Disease," <i>Hum. Hered.</i> 50:91-101, S. Karger AG (March-April 2000).
	AT	9	Hardy, J., "Amyloid, the presenilins and Alzheimer's disease," <i>Trends Neurosci.</i> 20:154-159, Elsevier Science, Ltd. (April 1997).

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	AR	<u>10</u>	Hollenbach, E. et al., "Confirmation of an association between a polymorphism in the exon 3 of the low-density lipoprotein receptor-related protein gene and Alzheimer's disease," <i>Neurology</i> 50:1905-1907, Lippincott-Raven Publishers (June 1998).
	AS	<u>10</u>	Horvath, S. and Laird, N.M., "A Discordant-Sibship Test for Disequilibrium and Linkage: No Need for Parental Data," <i>Am. J. Hum. Genet.</i> 63:1886-1897, University of Chicago Press (December 1998).
	AT	<u>10</u>	Hu, C-J. et al., "No association of alpha-2 macroglobulin gene five-nucleotide deletion with AD in Taiwan Chinese," <i>Neurology</i> 53:642-643, Lippincott, Williams & Wilkins (August 1999).

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	AL						Yes No
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	AN						Yes No
	AO						Yes No
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	AR	<u>11</u>	Hughes, S.R. et al., "α2-macroglobulin associates with β-amyloid peptide and prevents fibril formation," <i>Proc. Natl. Acad. Sci. USA</i> 95:3275-3280, National Academy Press (March 1998).
	AS	<u>11</u>	Jinnah, H.A. and Friedmann, T., "Gene therapy and the brain," <i>Br. Med. Bull.</i> 51:138-148, Oxford University Press (1995).
	AT	<u>11</u>	Justus, C.W.E. et al., "Quantification of free α2-macroglobulin and α2-macroglobulin-protease complexes by a novel ELISA system based on streptococcal α2-macroglobulin receptors," <i>J. Immunol. Methods</i> 126:103-108, Elsevier Science Publishers B.V. (1990).

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	AR	<u>12</u>	Kan, C-C. et al., "Nucleotide sequence of cDNA encoding human α 2-macroglobulin and assignment of the chromosomal locus," <i>Proc. Natl. Acad. Sci. USA</i> 82:2282-2286, National Academy Press (1985).
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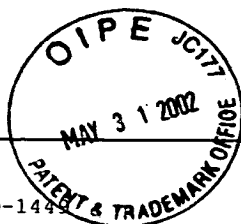
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	AR	<u>15</u>	Kovacs, D.M., "α2-Macroglobulin in late-onset Alzheimer's disease," <i>Exper. Gerontol.</i> 35:473-479, Elsevier Science, Inc. (July 2000).
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	AR	<u>17</u>	Lopes, M.B.S. et al., "Expression of α 2-macroglobulin receptor/low density lipoprotein receptor-related protein is increased in reactive and neoplastic glial cells," <i>FEBS Lett.</i> 338:301-305, Elsevier Science Publisher B.V. (1994).
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	AR	<u>18</u>	Marynen, P. et al., "A genetic polymorphism in a functional domain of human pregnancy zone protein: the bait region," <i>FEBS Lett.</i> 262:349-352, Elsevier Science Publishers B.V. (1990).
	AS	<u>18</u>	Matthijs, G. and Marynen, P., "A deletion polymorphism in the human alpha-2-macroglobulin (A2M) gene," <i>Nucleic Acids Res.</i> 19:5102, Oxford University Press (1991).
	AT	<u>18</u>	Misra, U.K. and Pizzo, S.V., "Binding of Receptor-recognized Forms of α 2-Macroglobulin to the α 2-Macroglobulin Signaling Receptor Activates Phosphatidylinositol 3-Kinase," <i>J. Biol. Chem.</i> 273:13399-13402, American Society for Biochemistry and Molecular Biology, Inc. (May 1998).

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	AR	19	Mori, T. <i>et al.</i> , " α 2-Macroglobulin is an astroglia-derived neurite-promoting factor for cultured neurons from rat central nervous system," <i>Brain Res.</i> 527:55-61, Elsevier Science Publisher B.V. (1990).
	AS	19	Myllykangas, L. <i>et al.</i> , "Genetic Association of α 2-Macroglobulin with Alzheimer's Disease in a Finnish Elderly Population," <i>Ann. Neurol.</i> 46:382-390, Lippincott, Williams & Wilkins (September 1999).
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	AS	20	Poller, W. et al., "Cloning of the human α 2-macroglobulin gene and detection of mutations in two functional domains: the bait region and the thiolester site," <i>Hum. Genet.</i> 88:313-319, Springer-Verlag (1992).
	AT	20	Poller, W. et al., "Sequence polymorphism in the human alpha-2-macroglobulin (A2M) gene," <i>Nucleic Acids Res.</i> 19:198, Oxford University Press (1991).

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	AT	<u>21</u>	Reeck, G.R. et al., "'Homology' in Proteins and Nucleic Acids: A Terminology Muddle and a Way out of It," <i>Cell</i> 50:667, Cell Press (1987).

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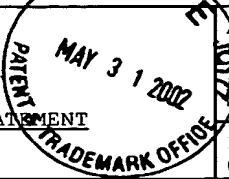
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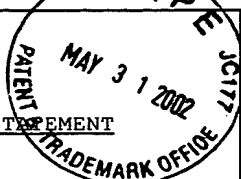
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	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	24	Sodeyama, N. et al., "α2-Macroglobulin polymorphism is not associated with AD or AD-type neuropathology in the Japanese," <i>Neurology</i> 54:443-446, Lippincott, Williams & Wilkins (January 2000).
	AS	24	Soto, C. et al., "Inhibition of Alzheimer's Amyloidosis by Peptides That Prevent β-Sheet Conformation," <i>Biochem. Biophys. Res. Commun.</i> 226:672-680, Academic Press, Inc. (September 1996).
	AT	24	Soto, C. et al., "β-Sheet breaker peptides inhibit fibrillogenesis in a rat brain model of amyloidosis: Implications for Alzheimer's therapy," <i>Nat. Med.</i> 4:822-826, Nature America, Inc. (July 1998).

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10/052,817APPLICANT
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01/23/2002GROUP
1632

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB- CLASS	FILING DATE
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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	25	Sottrup-Jensen, L. et al., "Primary Structure of Human α 2-Macroglobulin," J. Biol. Chem. 259:8318-8327, American Society of Biological Chemists, Inc. (1984).
	AS	25	Stratagene, 1988 Catalog, "Gene Characterization Kits," La Jolla, CA (February 1997).
	AT	25	Strauss, S. et al., "Detection of Interleukin-6 and α 2-Macroglobulin Immunoreactivity in Cortex and Hippocampus of Alzheimer's Disease Patients," Lab. Invest. 66:223-230, Lippincott, Williams & Wilkins (1992).

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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	26	Strickland, D.K. et al., "Sequence Identity between the α 2-Macroglobulin Receptor and Low Density Lipoprotein Receptor-related Protein Suggests That This Molecule Is a Multifunctional Receptor," <i>J. Biol. Chem.</i> 265:17401-17404, American Society for Biochemistry and Molecular Biology, Inc. (1990).
	AS	26	Strickland, D.K. et al., "Primary Structure of α 2-Macroglobulin Receptor-associated Protein. Human Homologue of a Heymann Nephritis Antigen," <i>J. Biol. Chem.</i> 266:13364-13369, American Society for Biochemistry and Molecular Biology, Inc. (1991).
	AT	26	Tanzi, R.E. et al., "Amyloid β protein Gene: cDNA, mRNA Distribution, and Genetic Linkage Near the Alzheimer Locus," <i>Science</i> 235:880-884, American Association for the Advancement of Science (1987).

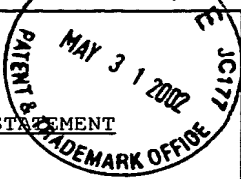
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		APPLICANT Tanzi et al. FILING DATE 01/23/2002 GROUP 1632	

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	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	27	Tanzi, R.E., "A genetic dichotomy model for the inheritance of Alzheimer's disease and common age-related disorders," <i>J. Clin. Invest.</i> 104:1175-1179, American Society for Clinical Investigation (November 1999).
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	AT	27	Tooyama, I. et al., "Immunohistochemical Study of $\alpha 2$ Macroglobulin Receptor in Alzheimer and Control Postmortem Human Brain," <i>Mol. Chem. Neuropathol.</i> 18:153-160, Humana Press, Inc. (1993).

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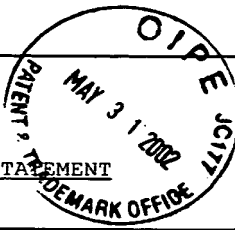
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	AO						Yes No
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	AR	28	Van Gool, D. et al., "α2-Macroglobulin Expression in Neuritic-Type Plaques in Patients with Alzheimer's Disease," <i>Neurobiol. Aging</i> 14:233-237, Pergamon Press, Ltd. (1993).
	AS	28	Van Leuven, F. et al., "The Receptor-binding Domain of Human α2-Macroglobulin. Isolation after Limited Proteolysis with a Bacterial Proteinase," <i>J. Biol. Chem.</i> 261:11369-11373, American Society of Biological Chemists, Inc. (1986).
	AT	28	Verpillat, P. et al., "α2-Macroglobulin Gene and Alzheimer's Disease: Confirmation of Association by Haplotypes Analyses," <i>Ann. Neurol.</i> 48:400-402, Lippincott, Williams & Wilkins (September 2000).

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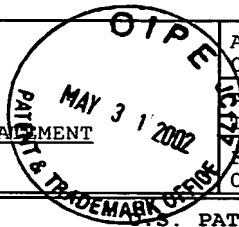
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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

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AR	29	Wavrant-DeVrière, F. et al., "Association between the low density lipoprotein receptor-related protein (LRP) and Alzheimer's disease," <i>Neurosci. Lett.</i> 227:68-70, Elsevier Science Ireland, Ltd. (May 1997).
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AT	29	Zhang, Z. et al., "Inhibition of α 2-macroglobulin/proteinase-mediated degradation of amyloid β peptide by apolipoprotein E and α 1-antichymotrypsin," <i>Int. J. Exp. Clin. Invest.</i> 3:156-161, Parthenon Publishing (September 1996).

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	AL2						Yes No
	AM2						Yes No
	AN2						Yes No
	AO2						Yes No
	AP2						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AR	30	Zill, P. et al., "Polymorphisms in the α 2-macroglobulin gene in psychogeriatric patients," <i>Neurosci. Lett.</i> 294:69-72, Elsevier Science Ireland, Ltd. (November 2000).
AS	30	International Search Report for International Application No. PCT/US00/02412, mailed July 6, 2000.
AT	30	Copy of co-pending U.S. Application No. 60/337,434, Becker et al., filed November 9, 2001.

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